UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,518	02/27/2004	Joan S. Steffan	00047	7728

71897 7590 08/05/2008

KAUTH , POMEROY , PECK & BAILEY ,LLP
P.O. BOX 19152
IRVINE, CA 92623

EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
08/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/789,518
Filing Date: February 27, 2004
Appellant(s): STEFFAN ET AL.

John W. Peck
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 21 May 2008 appealing from the Office action mailed 26 July 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

Appellant's brief presents arguments relating to objection to claim 19. This issue relates to petitionable subject matter under 37 CFR 1.181 and not to appealable subject matter. See MPEP § 1002 and § 1201.

However, solely to expedite prosecution and simplify the issues, the objection is withdrawn in view of Appellant's persuasive argument.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Melchior F, Annu Rev Cell Dev Biol 16: 591-626, 2000

Muller et al., Nature 2: 202-210

Feigin et al., Curr Opin Neurol 15: 483-489, 2002

Wang et al. Acta Pharmacologica Sinica, 27(10): 1287-1302, 2006

Ihara et al., JBC 282, 16465-16475, 2007

Melchior et al, TIBS 28: 612-618, 2003

Marsh et al. Neuron 52, 169-178, 2006

Agrawal et al. PNAS 102: 3777-3781, 2005

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 USC § 112-Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

2. The specification does not reasonably provide enablement for treating Huntington's disease (HD), in a patient diagnosed with HD, comprising administering a therapeutically effective, SUMO isopeptidase enhancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

3. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

4. The claims are drawn to a method for treating Huntington's disease, in a patient, comprising administering a therapeutically effective amount of a SUMO isopeptidase enhancer.

5. The specification of the instant application teaches that long repeats of polyglutamine (polyQ) in specific disease genes result in neurodegenerative disorders, for example Huntington's Disease (page 12, lines 18-21). The specification also teaches that mutant proteins and/or pathogenic polyQ polypeptides form aggregates in the nucleus and cytoplasm of neurons in Huntington's Disease (page 1, lines 23-27). Further the specification teaches that a truncated portion of the mutant Huntingtin protein (Httex1p) causes Huntington's disease like disorder in mice and flies (page 12, lines 21-24). The specification further demonstrates that SUMOylation is a post-translational modification system in which SUMO-1 covalently attaches lysine residues and modifies protein function (page 2, lines 15-26). Additionally the specification suggests that prevention SUMOylation of proteins by deSUMOylation enhancers could prove as potential treatments for neurodegenerative disorders. However, the specification does not disclose any methods or working examples to indicate a method for treating a patient diagnosed with HD, comprising administration of any SUMO isopeptidase enhancer.

6. Undue experimentation would be required by one skilled in the art to treating patients with HD. Undue experimentation would also be required of the

skilled artisan to identify and administer all possible SUMO isopeptidase enhancers.

7. Relevant literature of the art teaches that SUMO, also called PIC1, Ubl1, sentrin, GMP1 etc., may function as an antagonist to ubiquitin and is useful in protein degradation (Melchior F, Annu Rev Cell Dev Biol 16: 591-626, 2000, page 591; page 593). The art also teaches that SUMO-1 is a 101 amino acid polypeptide (Muller et al., Nature 2: 202-210). Muller et al., further teach that SUMOylation is a reversible process, leading to deSUMOylation, wherein SUMO is excised from the target protein, a reaction catalyzed by isopeptidases (page 202-203, "SUMO deconjugation"). The prior art further teaches that SUMO processing enzymes, having isopeptidase activity and belonging to a family of related proteins, have been characterized from humans and yeast (Melchior et al. see page 602, para 1). However, relevant literature does not teach the treating of HD patients with a deSUMOylation enhancer. Furthermore, it is well known in the art that HD is proven to be recalcitrant to treatment (Feigin et al., Curr Opin Neurol 15: 483-489, 2002). Therefore, one skilled in the art would not be able to predict from the instant specification that all possible deSUMOylation enhancers, including SUMO isopeptidase, would be able to treat a complex disease like HD. Undue experimentation would be required to determine such.

8. Furthermore, the instant specification teaches the use of a Drosophila model for Huntington's Disease, which after crossing with the reduced function Drosophila SUMO mutant (*smt3*), results in the suppression of

neurodegeneration (page 3, lines 24-27; page 27, lines 22-32; Figure 5A). The specification further demonstrates that decreased levels of SUMOylation results in the lowering of photoreceptor neuron degeneration in the fly model, induced by the Huntingtin gene (page 3, lines 9-12); thereby suggesting that a reduction of SUMO-1 modification may prove to be useful for treatment of Huntington's disease. However, to test for treatment of a disease in a subject, one would need to conduct studies on non-human mammals that would more closely replicate the essential features of the pathophysiology of the disease in humans, as compared to invertebrate models. As Wang et al. (Acta Pharmacologica Sinica, 27(10): 1287-1302, 2006) suggests that the "proof of efficacy in mammalian models is considered a prerequisite before considering possible testing in humans" (page 1297, column 2, para 2). Wang et al., further teach that since flies "are not accessible to externally administered drugs", the studies should be conducted in a mammalian model to get a better expression of the disease and "response to potential therapies" (see page 1295, column 1, para 2; page 1297, column 1, para 1). However, neither the specification of the instant application, nor the prior/post art literature teach any methods or working examples that indicate administration of any SUMO isopeptidase enhancer for treatment in humans. As the molecular processes of pathogenesis of Huntington's disease are yet to be fully uncovered, the success of treatment or identifying such patient at risk would be unpredictable, thus the invention would entail undue experimentation by a skilled artisan.

9. Due to the large quantity of experimentation necessary to treat HD by administration of any SUMO isopeptidase enhancer; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which has yet to determine a suitable model for treatment of Huntington's Disease and, the unpredictability of using invertebrate models for actual treatment in humans, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

(10) Response to Argument

10. Appellant categorizes the argument of the enablement rejection on 2 major issues of the rejection as follows:

(i) Insufficient disclosure to enable the use of all possible SUMO isopeptidases to treat Huntington's Disease (HD)

(ii) Fly model is not sufficient to enable methods of treatment of human patients with HD with drugs that affect SUMO isopeptidase

11. (i) Non-enablement for treating HD with all possible SUMO isopeptidases:

At the onset, Appellant clarifies that the instant invention is directed to treatment methodology of HD by administration of SUMO isopeptidase

enhancers, thereby enhancing deSUMOylation and treating HD, not SUMO isopeptdisases as addressed by Examiner in the rejection under appeal. Based on studies in the instant specification and in the relevant literature, Appellant asserts that "a reduced function *smt3* [Drosophila SUMO] mutant results in a suppression of lethality and of neurodegeneration" with regards to HD. Additionally, Appellants assert that the enhancement of deSUMOylation, using increased levels of SUMO isopeptidase reduces polyglutamine toxicity, further indicating a therapeutic effect in polyglutamine repeat diseases such as HD. Appellants firmly believe that the "detailed and focused" results presented in the instant application, being an outcome of studies on "organisms specifically designed to model the physiological impacts of Huntington's Disease", would undoubtedly lead a person of ordinary skill in the art, to administer agents that would enhance the SUMO isopeptidase activity in HD patients as a therapeutic without undue experimentation. Additionally, Appellants allege that the Examiner did not provide any argument or evidence on the issue of undue experimentation to determine appropriate SUMO isopeptidase enhancers for the claimed purpose. Appellants point out that the test of enablement is not whether the instant specification discloses how to "treat humans using every SUMO isopeptidase enhancer", rather whether "one of ordinary skill in the art would have been able to develop therapeutic treatments". Each of the arguments will be considered in the following paragraphs.

12. Appellant's arguments have been fully considered but have not been found to be persuasive. Relevant state of the art teaches that SUMO proteases or isopeptidases bind to SUMO non-covalently (Ihara et al., JBC 282, 16465-16475, 2007). About 5 mammalian SUMO hydrolases, having isopeptidase activity are known (Melchior, Ann Rev Cell Dev Biol 16: 591-626, 2000; pages 601-602; Melchior et al, TIBS 28: 612-618, 2003; Table 2), each having different target specificities and subcellular localization, e.g. nucleoplasm, nucleolus, cytoplasm, cytoplasmic vesicles etc. (Melchior et al. page 614, col 2, para 2; Figure 2). Furthermore, each of the isopeptidases have various isoforms that vary within the same species in their N-terminal domain, that further determines their intracellular localization. Based on the state of the art at the time of filing the instant application and knowing the existence of more than 50 SUMO targets, Melchior et al. further pointing to the complex network of modifying and demodifying enzymes, states that "there will not be a simple unifying theme for the functions of SUMO" (page 617, concluding para).

13. The instant specification teaches that the expression of a truncated portion of the mutant Htt protein encoded by exon 1of the HD gene (Httex1p) results in a pathogenesis that is similar to HD in transgenic mice and flies (page 3, lines 18-22). The instant specification on page 2, also teaches that SUMOylation is a post-translational modification system, wherein SUMO-1 modifies its target protein by non-covalently attaching to lysine residues in the cellular nucleus (lines 15, 20-22, 31-35). On page 13 of the specification (lines 8-15), Appellant

demonstrates improved neuropathology with decreased SUMO levels based on data provided in the Drosophila model, wherein crossing of the fly model of HD with a reduced function Drosophila SUMO gene (*smt3*), exhibited suppressed lethality and neurodegeneration of the eye photoreceptor neurons (Figure 5, page 10, lines 22-36). Furthermore, using HeLa cells and striatal neurons in culture, Httex1p is modified by SUMO-1 on lysines 6, 9, and 15, mutations of the said lysine residues to arginine resulted in reduced protein stability (page 21, lines 8-11; page 3, lines 18-23; Figure 1A and C), thereby demonstrating the protective effect of blocking the attachment of SUMO to its target protein. Based on the above findings, Appellant suggests that "blockage of the process of SUMOylation of proteins or enhancement of the process of deSUMOylation of proteins *may* prevent neurodegeneration and death caused by polyglutamine repeat diseases" (emphasis added by examiner implying uncertainty) (instant specification, page 13, lines 16-26). However, as adjudged from the genus of SUMO isopeptidases and their isoforms, their differences in target specificities, different subcellular localizations, the inadequate knowledge in these directions in the state of the art, the instant specification fails to provide sufficient guidance to one skilled in the art to make and use the appropriate an SUMO isopeptidase enhancer for treating a complex disease such as HD with success and predictability in a patient. Additionally, no guidance or working examples are provided in the instant specification with regards to enhancing deSUMOylation by the administration of a SUMO isopeptidase enhancer.

14. At page 7 and 8, para 2, Appellant argues that the Drosophila model, corresponding to "organisms specifically designed to model the physiological impacts of Huntington's Disease" was used to study the therapeutic effect of enhanced SUMO isopeptidase activity. Appellants further argue that the "test is not whether the specification contains an actual disclosure of how one of ordinary skill in the art would treat humans using every SUMO isopeptidase enhancer, only whether one of ordinary skill in the art would have been able to develop therapeutic treatments without undue experimentation". Appellants allege that Examiner has not provided any argument or evidence to support the rejection based on undue experimentation to determine the appropriate SUMO isopeptidase enhancer for the claimed method. Appellant's arguments are considered but not found to be persuasive for reasons explained above. Additionally, the studies in the instant specification provide data geared towards blocking of SUMOylation, not stimulating detachment of SUMO from its target protein or deSUMOylation. This is in agreement with Appellant's emphasis at page 7 of the Brief, which states that "decreased SUMOylation decreases neurodegeneration from Huntington's Disease" in a fly model (which is interpreted as decreased attachment of SUMO versus the claimed increased detachment of SUMO). The skilled artisan will not be able to extrapolate the effects of the disclosed blockage of SUMOylation to the claimed invention of enhanced deSUMOylation, since these involve different cascades of biochemical reactions and physiological events.

15. Moreover, Appellant's emphasis on the Drosophila model for HD treatment is not persuasive. As repeatedly asserted by Appellant on various responses and amendments in the past and in the current Brief, Examiner agrees that the fly model is an important model to study neurodegenerative diseases and for screening of therapeutics for such diseases. However, knowing the state of the art of SUMO isopeptidase and the complexities of HD, lack of available treatment options at the time of filing, insufficient guidance in the specification, no knowledge about the isopeptidase enhancers, a leap from the fly model to treat human patient with HD would be highly unpredictable and result in undue experimentation. More detailed response towards the use of the Drosophila model for human treatment will follow in the next section.

16. Furthermore, in making a determination of whether the application complies with the enablement requirement of 35 U.S.C. 112 first paragraph, each claimed invention must be evaluated to determine whether there is sufficient guidance provided and supported by working examples to inform a skilled artisan how to use the claimed invention without undue experimentation. In the instant case, the specification provides no guidance on how to use the claimed method for the treatment of HD in a patient because there is no evidence or sound scientific reasoning presented in the case, that administration of a SUMO isopeptidase enhancer would be beneficial to treat HD in a patient. Even if Appellant's prophecy of the importance of enhancing deSUMOylation in HD is accepted, there is no evidence that administration of any SUMO isopeptidase

enhancer in a HD patient would successfully treat the disease, since there are multiple processes that contribute to the development of HD. Appellant's prophetic suggestion of treating HD by enhancing deSUMOylation in a patient constitutes an invitation to experiment by trial and error. As was found in *Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987)*, a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most biochemical reactions and physiological activity, especially in the treatment of chronic, complex, debilitating and lethal neurodegenerative diseases like HD. One skilled in the art would not be able to predict from the instant specification or the state of the prior and post art, that enhancers to all possible SUMO isopeptidases will be therapeutically effective in treating HD. As stated in the MPEP (2164.03) "if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (*Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004)).* The specification fails to provide adequate details towards the claimed invention so as to enable a skilled artisan to make and use the invention without undue experimentation.

17. At page 6 (para 3), Appellant clarifies the subject matter of the claims to be relying on the administration of SUMO isopeptidase enhancer, not "SUMO isopeptidases" as discussed in Examiner's rejection. Although Examiner

acknowledges that SUMO isopeptidase, but not SUMO isopeptidase enhancer was considered in the previous rejections, the issue still remains the same. In other words, based upon arguments presented above, a skilled artisan would not be able to successfully select an enhancer without the proper knowledge and guidance to the appropriate SUMO isopeptidase, administer the same in a therapeutically effective amount in a HD patient for treating the disease, without undue experimentation. In the absence of adequate guidance from the specification, the practitioner would need to fall back upon undue trial and error experimentation to make/use any isopeptidase enhancer for the claimed treatment method.

18. (ii) Adequacy of Appellant's Drosophila Model

Although Appellants concede at the very beginning that "it is well-established that prior to human testing mammalian models are not only needed, but mandated by law" Appellants emphatically allege that Examiner's legal test neither comports with the enablement requirements set forth by the Courts nor complies with the standard provided by the Manual of Patent Examination Practice (MPEP). Appellants specifically point to the MPEP Section 2164.02 stating that a "working example" (in this case a therapeutic model) is not necessary. Appellants further assert that despite providing working examples using a HD fly model, including "data on the efficacy of a SUMO isopeptidase

enhancer in treating HD", Examiner has "set mammalian tests as a threshold for enabling a therapeutic claim" a stand not legally supported. Appellants raise the issue of "correlation", citing MPEP paragraphs and case laws, accentuating the argument that neither MPEP nor the courts require "an exact correlation between the examples and the claimed invention as long as the particular model is "recognized as correlating"". Appellants repeatedly emphasize the importance of the fly model used with the claimed therapeutic in the examples of the instant application, as well as reminds the significance of other fly models in neurodegenerative disorders that was provided in the 4/10/07 Amendment. Finally, highlighting Examiner's agreement that the Drosophila fly model is "extensively used for studying different aspects of neurodegenerative diseases, and is a cost-effective platform for testing large matrices of drug combinations" and because Examiner only provided a single reference (Wang et al) disputing the validity of the fly model in the instant invention, Appellant alleges that there is a "reasonable correlation between Appellant's tests and a therapeutic treatment". In conclusion, Appellant cautions that upholding the dismissal of working examples would "improperly raise the enablement standard for claims to human treatments far in excess of the standard set forth by the courts". Appellant, therefore requests that the rejection of claim 19 under 35 U.S.C. § 112 ¶ 1 should be withdrawn.

19. Appellant's arguments directed to the claimed invention have been fully considered but have not been found to be persuasive. Specifically Appellant has

repitatively argued over the validity of the Drosophila fly model in the claimed method of treatment of HD in patients. At page 9, para 2, Appellant cites MPEP (2164.02) and alleges that a working example in the form of a therapeutic model is not necessary and further argues that Appellants have provided a number of working examples with a fly model to support the claimed invention. At page 11, para 2, Appellant reiterates the use of the fly model in the instant specification to show the efficacy of the claimed therapeutic. Furthermore, at page 11, para 2, Appellant consolidates the assertion of the adequacy of the fly model based on Examiner's acknowledgement of the validity of the Drosophila as a model for studying neurodegenerative diseases. Examiner agrees that compliance with the enablement requirement is not based on whether a working example is disclosed in the specification. Nonetheless, as stated in the MPEP, "lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art" (2164.02). As stated above, it is reiterated that HD is a complex progressive neurodegenerative disease, wherein the mechanisms underlying neuronal death are largely unknown (Feigin et al., Curr Opin Neurol 15: 483-489, 2002). Additionally, it is well known in the art that many neurodegenerative diseases like HD, are proven to be recalcitrant to treatment. Furthermore, as explained supra, the state of the art with respect to SUMO isopeptidase and enhancers thereof is premature. However, neither the specification of the instant application, nor the prior/post art literature teach any methods or working examples that indicate administration of any deSUMOylation

enhancer for treatment in humans. As the molecular processes of pathogenesis of Huntington's disease are yet to be fully uncovered, the success of treatment would be unpredictable, thus the invention would entail undue experimentation by a skilled artisan.

20. Examiner again acknowledges that the Drosophila fly model is extensively used for studying different aspects of neurodegenerative diseases in humans, and that the fly expresses genes that mimic the pathology in mammalian systems. Examiner also agrees that the Drosophila provides a "cost-effective platform for testing large matrices of drug combinations". However, Examiner does not agree with the Appellant's argument that the fly model can be used for determining a method of treatment of HD in humans. To test for treatment of a disease in a subject, one would need to conduct studies on non-human mammals that would more closely replicate the essential features of the pathophysiology of the disease in humans versus invertebrate models. It is universally accepted, and also acknowledged by Appellant on page 9, para 2 of the Brief, that prior to human testing, a mammalian model is mandated by law. As Wang et al. (Acta Pharmacologica Sinica, 27(10): 1287-1302, 2006) suggests that for treatment purposes, "the proof of efficacy in mammalian models is considered as a prerequisite before considering possible testing in humans". Wang et al., further teach that since flies "are not accessible to externally administered drugs", the studies should be conducted in a mammalian model to

get a better expression of the disease and "response to potential therapies" (see page 1295, column 1, para 2; page 1297, column 1, para 1).

21. The Drosophila model is more important as a pre-screen for testing and identifying drugs for the treatment, not for treatment *per se* of complex neurodegenerative diseases, like HD in humans. Ample evidence in the relevant literature, including the citations provided by the Applicants in the amendments dated 4/10/07 corroborate this assertion. For example: Marsh et al (Neuron 52, 169-178, 2006; concluding para, page 175) state that, ".....allow fly studies to speed the progress of identifying promising therapeutic strategies for testing in manmals" (emphasis added). Agrawal et al. (PNAS 102: 3777-3781, 2005; col 1, last para) state that, "Drosophila.....for testing large matrices of drug combination for optimal combinations of therapeutic drugs, and to test for undesirable interactions, before proceeding to mouse models or patients suffering from HD". ....(emphasis added). Agrawal et al. also state that "Preclinical in vivo testing strategies such as those described here (in the fly) could result in a great savings of cost and time in developing potential disease treatments and can serve to identify treatment regimens that are very likely to provide therapeutic benefit to patients". (page 3781, concluding para).

22. At page 10, Appellant argues the issue of correlation emphasizing that the MPEP or the courts do not require "an exact correlation between the examples and the claimed invention as long as the particular model is recognized as correlating". Appellants provide case laws to support this contention. Appellant's

arguments are fully considered, but not found to be persuasive. As detailed supra, the specification and the relevant art has failed to provide sufficient guidance in making and using the claimed invention. It is accepted that the fly model is an important model for studying the neurodegenerative diseases, and for identifying therapeutics for the treatment of such diseases. However, a person skilled in the art would not be able to extrapolate the results from the fly to a human, especially in case of treatment of HD, which is complicated for reasons stated above. A similar apprehension is also presented by Feigin et al. after the failure of neuroprotective effect of compounds in a HD human trial. Based on this finding, Feigin et al. state that "positive results from animal models of Huntington's Disease need to be viewed with caution, and that careful clinical trials will be required to adequately evaluate drugs that appear promising in animal models" (page 488, col 2, para 2). With the observed unpredictability in the treatment of HD, administering any enhancer of any SUMO isopeptidase in a human patient, would thus entail undue experimentation. Appellant's citing of case laws asserting utility requirements is uncalled for, because the instant rejection does not dispute utility.

23. At page 11, last para, Appellant, in support of the fly model, quotes Wang et al's statement which suggest that "by every measure flies expressing mutant human genes present with pathology that mimics the human disease in every important way". Appellant's point is noted, however, Wang et al. continue by saying that "how to make Drosophila models more amenable to high-throughput

and automated screening for therapeutics is an important issue. …….flies are not accessible to externally administered drugs". Therefore, once again Wang et al's statement confirms that the Drosophila is an important model reflecting a pathology of the human disease, however, is largely considered for high-throughput screening of therapeutics, not for the treatment of human patients.

24. At page 12, para 1, Appellants repeat the allegation that Examiner does not provide any prior art that questions the validity of the fly model, therefore, the working example of the fly is proper and commensurate to the claimed invention, and the Examiner's contention is unwarranted and improper. Appellant further cautions that in the event of such rejection being upheld, would "improperly raise the enablement standard for claims to human treatments far in excess of the standard set forth repeatedly by the courts".

25. Appellant's arguments are fully considered, however, are not found to be persuasive for reasons detailed supra. Examiner has provided valid reasoning supported by peer-reviewed literature to explain the limitations of the fly model. On account of the lack of sufficient knowledge or guidance with regards to the SUMO isopeptidases and the enhancers thereof, combined with the complexity of HD pathology, the instant specification fails to enable a skilled artisan to make and use the invention without undue experimentation. Therefore, the invention does not meet the enablement standard for human treatment set by the courts.

26. In Section 4 of the Argument, Appellant concludes by restating that the specification provides sufficient disclosure that would enable a skilled artisan to

make or use the claimed invention, thus requesting the rejection under 35 U.S.C. § 112, first paragraph to be withdrawn.

27. Appellant's arguments are fully considered, however, not found to be persuasive for all the above reasons. The disclosure is insufficient to teach one of skill in the art how to make or use the invention for reasons explained above. As is evidenced in the discussions supra, each of Appellants arguments have been carefully considered and it is maintained that undue experimentation would be required by the skilled artisan to make or use the instant invention, thereby maintaining the rejection under appeal.

28. Specifically, proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to treat HD by administration of any SUMO isopeptidase enhancer; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which has yet to determine an ideal model **for treatment** of Huntington's Disease in a patient and, the unpredictability of using invertebrate models for actual treatment in humans, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

(11) Related Proceeding(s) Appendix

29. No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Aditi Dutt/

Examiner, Art Unit 1649

Conferees

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649

/Robert Wax/

TC1600 Appeals Specialist